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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/998,904	GARNER ET AL.	
	Examiner	Art Unit	
	LARRY D. RIGGS II	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,9-42,44-53,56,57,203 and 204* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,9-42,44-53,56,57,203 and 204* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments filed 14 March 2009 are acknowledged.

Status of Claims

Claims 4, 8, 43, 54, 55, 58-202 and 205-213 are cancelled. Claims 1-3, 5-7, 9-42, 44-53, 56, 57, 203 and 204 are currently pending and under consideration.

Withdrawn Rejections/Objections

The objection to claims 18 and 19, in the Office action mailed 14 August 2008 is withdrawn in view of the amendments filed 14 March 2009.

The rejection of claims 1-3, 5-7, 9-42, 44-53, 56-57 under 35 U.S.C. 101, in the Office action mailed 14 August 2008 is withdrawn in view of the amendments filed 14 March 2009.

The rejection of claims 1, 45 and 46 under 35 U.S.C. 102(b) over Shapiro et al., in the Office action mailed 14 August 2008 is withdrawn in view of the amendments filed 14 March 2009.

The rejection of claims 2, 3, 5-7, 9, 10 and 37 under 35 U.S.C. 103(a) over Shapiro et al. in view of Levy et al., in the Office action mailed 14 August 2008 is withdrawn in view of the amendments filed 14 March 2009.

The rejection of claim 11 under 35 U.S.C. 103(a) over Shapiro et al. in view of Levy et al., in view of Lippa et al., in the Office action mailed 14 August 2008 is withdrawn in view of the amendments filed 14 March 2009.

The rejection of claim 12 under 35 U.S.C. 103(a) over Shapiro et al. in view of Levy et al., in view of Reiter et al., in the Office action mailed 14 August 2008 is withdrawn in view of the amendments filed 14 March 2009.

The rejection of claims 13-21, 47, 48, 52 and 56 under 35 U.S.C. 103(a) over Shapiro et al. in view of Levy et al and further in view of Smigielski et al., in the Office action mailed 14 August 2008 is withdrawn in view of the amendments filed 14 March 2009.

The rejection of claims 53, 57, 203 and 204 under 35 U.S.C. 103(a) over Shapiro et al., in the Office action mailed 14 August 2008 is withdrawn in view of the amendments filed 14 March 2009.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The instant rejection is newly applied in-part and maintained and reiterated in-part from the previous office action, mailed 14 August 2008.

Claims 1-3, 5-7, 9-42, 44-53, 56, 57, 203 and 204 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The instant claims 1-3, 5-7, 9-42, 44-53, 56, 57, are drawn to a method for predicting one or more locations of single nucleotide polymorphisms in a nucleic acid sequence. The instant claims are drawn to the abstract process steps of calculating a variation frequency, generating a variation predictiveness matrix, comparing the nucleic acid sequence, identifying where polymorphisms will likely occur and outputting the identified locations to a user via a computer display, electronic file or printer.

The Supreme Court has enunciated a definitive test to determine whether a process claim is tailored narrowly enough to encompass only a particular application of a fundamental principle rather than to pre-empt the principle itself. A claimed process is surely patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing. See in re Bilski 88 USPQ2d 1385 (Fed. Cir. 2008) and in re Comiskey 89 USPQ2d 1655 (Fed. Cir. 2009). See also Benson, 409 U.S. at 70; Diehr, 450 U.S. at 192; see also Flook, 437 U.S. at 589 n.9; Cochrane v. Deener, 94 U.S. 780, 788 (1876).

The instant claims do not recite or inherently involve any transformation of an article, therefore the Examiner must determine if the instant claims have a tie to a particular machine or apparatus. The instant claims do not recite any limitation that ties the recited abstract process to any particular machine or apparatus. Outputting or displaying said locations are an insignificant extra-solution activity. Neither the storing of data nor displaying of data is critical to the invention of identifying locations of where polymorphisms will likely occur, for storing and displaying only preempt the noted abstract process. Nominal or token recitations will not suffice, E.g. displaying, inputting,

obtaining, See Ex parte Langemyr (May 28, 2008). Applicants are cautioned against introduction of new matter in an amendment.

Claims 203 and 204 are drawn to a computer readable medium comprising a computer program executable by a processor for predicting one or more locations of variations in a sequence. While the instant specification does not explicitly define the scope of the limitation of "computer readable medium," one skilled in the art would understand that computer readable medium includes carrier wave, which is a signal. See, e.g., In re Nuitjen, Docket no. 2006-1371 (Fed. Cir. Sept. 20, 2007)(slip. op. at 18)("A transitory, propagating signal like Nuitjen's is not a process, machine, manufacture, or composition of matter.' … Thus, such a signal cannot be patentable subject matter.").

Therefore, at least one embodiment of the instant claims 203 and 204 are drawn to carrier wave or a signal encoded thereon a computer program.

Response to Arguments

Applicant's arguments filed 14 March 2009 have been fully considered and are persuasive in part.

Applicants argue that the concrete, useful and tangible test is inappropriate for the instant method claims 1-3, 5-7, 9-42, 44-53, 56, 57, but that the machine-or-transformation test from In re Bilski applies. Applicants argue the instant method claims meet the machine-or-transformation test because the raw data is transformed into a visual depiction. Applicants argue the instant computer-readable medium claims (203

and 204), are structurally and functionally interrelated to the medium and is statutory because the use of technology ("executable by a processor") permits the function of the descriptive material to be realized, pursuant to MPEP § 2106.01(i)(second paragraph) and that the computer program, as recited in the instant claims, is part of a computer that is executable by the computer's processor, so the claim is directed part of a machine (i.e. a processor of a computer).

Regarding the concrete, useful and tangible test, applicant's arguments are persuasive.

Regarding applicants' remaining arguments, they are not persuasive.

Applicant's instant method claims do not perform a transformation of a particular article. The facts in In re Abele pertained to analog data transformed to digital data via an algorithm yielding a visual depiction of bone. Visualizing SNP locations on a display does not match the fact pattern as set forth in In re Abele and the instant visualization step is insignificant post-solution activity. See above. Likewise, there is no tie of the instant method to a particular machine.

As set forth in the previous Office action and reiterated above, a claim reciting only a signal, (at least one embodiment of claims 203 and 204), does not appear to be a process, machine, manufacture, or composition of matter. See, e.g., In re Nuitjen, Docket no. 2006-1371 (Fed. Cir. Sept. 20, 2007)(slip. op. at 18)("A transitory, propagating signal like Nuitjen's is not a process, machine, manufacture, or composition of matter.' … Thus, such a signal cannot be patentable subject matter."). Likewise, a computer readable medium encoded with a computer program executable by a

processor is only a medium with code with the intended use of be executed by a computer. Embodiments of the computer readable medium read on a signal.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. (Journal of Immunology, 1999, 163, 259-268) in view of Storb et al. (Phil. Trans. R. Soc. Lond. B., 2001, 356, 13-19).

The instant claim 1 provides a computer-implemented method for predicting one or more locations of single nucleotide polymorphisms in a nucleic acid sequence, comprising the steps of: calculating a variation frequency from a first base to a second base within a group of bases in a dataset of two or more genes; generating a variation predictiveness matrix from the calculated variation frequency for each first base to each second base; comparing the nucleic acid sequence which is not obtained from the dataset of two or more genes, one or more bases in the nucleic acid sequence at a time, with the variation predictiveness matrix to assign a variation value to the one or more bases in the nucleic acid sequence; identifying the locations of the one or more bases in the nucleic acid sequence where single nucleotide polymorphisms will likely occur based on the assigned variation value; and outputting the identified locations of the single nucleotide polymorphisms in the nucleic acid sequence where single nucleotide polymorphisms will likely occur to a user via a computer display, an electronic file or a printer.

Regarding claim 1, Shapiro et al. shows oligonucleotide mutability indexes between bases, i.e. the number of times given a oligonucleotide within a segment of DNA contained a mutation divided by the number of times the oligonucleotide was expected to be mutated, (page 260, left column, last paragraph – right column, first paragraph; Tables I and II). Shapiro et al. shows a predicted composite mutability index

for a region or nucleotides by determining the number of times each di- or trinucleotide occurred within each region of each gene and multiplying by its mutability index, (page 260, right column, second paragraph). Shapiro et al. shows comparing nucleic acid sequences with a composite regional mutability index, providing regions that would be most (mutability indexes >1) or least mutable, CDR1 and CDR2 in both murine and human V_H genes were predicted to mutate the most, wherein these regions of predicted regional mutability are displayed (page 263; Figures 3-4; Table III). Shapiro et al. shows mutability frequency of one base with respect to a second base, (page 261, last paragraph – page 263, Table III). Shapiro et al. shows locations of where mutability will occur, wherein specific sequences and high mutability indexes would make it obvious to one skilled in the art where these specific base locations occur, (page 263, right column – page 264, left column, first paragraph; Table III).

Shapiro et al. does not show comparing the nucleic acid sequence which is not obtained form the dataset of two or more genes. However, Shapiro et al. shows that the shared hierarchy of di- and trinucleotide target immutabilities among H and L chain V genes in mice and humans suggest that a common mutation mechanism acts on all Ig genes of both species, (page 265, right column, first paragraph).

Storb et al. investigates target specificity of somatic hypermutation (SHM) in comparing mutation frequencies of IG and BCL-6 genes, (page 13, right column, second paragraph). Storb et al. shows determination of whether mutation in the BCL-6 gene was due to (SHM) and compared mutated nucleotides in BCL-6 to those in the Ig V_H genes and revealed that the same rules as those for Ig genes govern the targeting of

BCL-6 genes for SHM, (page 14, left column, last paragraph - page 15, left column, paragraph 2; Table 2). Storb et al. shows locations of likely mutation, (Table 3). BCL-6 genes were not used to produce the dataset of Shapiro et al. (Tables I-III).

Regarding claim 45, Shapiro et al. shows oligonucleotide mutability indexes between bases within bases from one to three at a time, (Tables 2-3).

Regarding claim 46, Shapiro et al. shows mutability indexes normalized for codon usage (page 260, right column, first and second paragraphs, pages 267-268; Figure 7).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method predicting mutability in Ig V genes by Shapiro et al. by comparing other genes expressed in B lymphocytes such as BCL-6 genes of Storb et al. because Shapiro et al. shows that the shared hierarchy of di- and trinucleotide target immutabilities among H and L chain V genes in mice and humans suggest that a common mutation mechanism acts on all Ig genes of both species, (page 265, right column, first paragraph) and a person of ordinary skill in the art would understand that target specificity of somatic hypermutation (SHM) may act similarly on genes that are expressed in B cells as taught by Storb, (page 13, right column, second paragraph) would result in identified locations of polymorphisms. Therefore, one of ordinary skill in the art would recognize the claimed process as a combination of routine applications that are well known the art that and produce no more than expected results.

Response to Arguments

Applicant's arguments filed 14 March 2009 have been fully considered but they are only persuasive in part.

Applicants argue that Shapiro et al. does not show calculating or matrix of variation frequency from a first base to a second base, comparing the nucleic acid sequence which is not obtained from the dataset of two or more genes and identifying locations of the one or more bases in the nucleic acid sequence where the single nucleotide polymorphisms will likely occur based on the assigned variation value.

Shapiro et al. does show calculating and matrix of variation frequency from a first base to a second base, see above. Shaprio et al. in view of Storb et al. shows identifying locations of one or more bases in a sequence where mutation will likely occur based on the mutability values, see above.

Claims 1-3, 5-7, 9, 10, 37, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. (Journal of Immunology, 1999, 163, 259-268) in view of Storb et al. (Phil. Trans. R. Soc. Lond. B., 2001, 356, 13-19) as applied to claims 1, 45 and 46 above, and further in view of Levy et al. (J. Exp. Med., 1988, 168, 475-489).

The instant claims 2-3 depend from claim 1 with the extra limitation that the nucleic acid sequence further comprises one or more chemical modifications including methylation or other chemical groups. The instant claims 5-6 depend from claim 1 with the extra limitation that a variation from the first base to the second base is non-

synonymous or synonymous. The instant claims 7, 9-10 depend from claim 1 with the extra limitation of a data set of SNPs or genes with chemical modifications. The instant claims 37-38 depend from claim 1 with the extra limitation that the nucleic acid comprises cDNA or a genomic sequence.

Shapiro et al. in view of Storb et al. is applied to claims 1, 45 and 46 above.

Shapiro et al. in view of Storb et al. do not show nucleic acid sequence further comprises one or more chemical modifications, variations from the first base to the second base being non-synonymous or synonymous, data set of SNPs or genes with chemical modifications, or nucleic acid comprises cDNA, or a genomic sequence.

Regarding claims 2 and 3, Levy et al. shows the nucleic acid sequence of V region genes containing methylation at the cytosine residues, e.g. CDR1 and CDR2, pointing to methylation and mutations within these regions, (page 484, page 486, third and fourth paragraphs, page 487, last paragraph; Figures 1-2).

Regarding claims 5 and 6, Levy et al. shows regions of mutation in nucleic acid sequence that is non-synonymous (CDR2 and CDR3) and synonymous (CDR1), (Figure 1; Tables 1-2).

Regarding claim 7, Levy et al. shows a table of single nucleotide polymorphisms for one or more nucleic acid sequences, (Tables 1-2).

Regarding claims 9-10, Levy et al. shows a table (dataset) of various V genes with known methylation at the cytosine residues, (page 484, page 486, third and fourth paragraphs, page 487, last paragraph; Figures 1-2; Tables 1-2).

Regarding claim 37, Levy et al. shows cDNA sequence of expressed human tumor V genes, (page 476, last paragraph; Figures 1-2).

Regarding claim 38, Levy et al. shows genomic sequence, (page 477, first paragraph of results).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method predicting mutability in Ig V genes by Shapiro et al. by comparing other genes expressed in B lymphocytes such as BCL-6 genes of Storb et al. and with the analysis of mutational regions of V genes with known methylation sites by Levy et al. because Shapiro et al. shows that the shared hierarchy of di- and trinucleotide target immutabilities among H and L chain V genes in mice and humans suggest that a common mutation mechanism acts on all Ig genes of both species, (page 265, right column, first paragraph) and a person of ordinary skill in the art would understand that target specificity of somatic hypermutation (SHM) may act similarly on genes that are expressed in B cells as taught by Storb, (page 13, right column, second paragraph) and the regions of nucleic acid with a tendency of mutation may be influenced by methylation of specific cytosine residues as shown by Levy et al., (page 487; Figures 1-2; Tables 1-2). Therefore, one of ordinary skill in the art would recognize the claimed process as a combination of routine applications that are well known the art that and produce no more than expected results.

Claims 1-3, 5-7, 9-11, 37, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. (Journal of Immunology, 1999, 163, 259-268) in

view of Storb et al. (Phil. Trans. R. Soc. Lond. B., 2001, 356, 13-19), further in view of Levy et al. (J. Exp. Med., 1988, 168, 475-489) as applied to claims 1-3, 5-7, 9, 10, 37, 45 and 46 above, and further in view of Lippa et al. (American Journal of Pathology, 1998, 153(5), 1365-1370).

The instant claim 11 depends from claim 1 with the extra limitation that the dataset of two or more genes comprises a dataset of known mutation dataset.

Shapiro et al. in view of Storb et al., in view of Levy et al. are applied to claims 1-3, 5-7, 9, 10, 37, 45 and 46 above.

Regarding claim 11, Shapiro et al. in view of Storb et al., in view of Levy et al. do not show a dataset of genes with known mutations.

Lippa et al. shows a dataset with genes with known mutations, (Table 1).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method predicting mutability in Ig V genes by Shapiro et al. by comparing other genes expressed in B lymphocytes such as BCL-6 genes of Storb et al., with the analysis of mutational regions of V genes with known methylation sites by Levy et al. and the use of a dataset of genes with known mutations by Lippa et al., because Shapiro et al. shows that the shared hierarchy of di- and trinucleotide target immutabilities among H and L chain V genes in mice and humans suggest that a common mutation mechanism acts on all Ig genes of both species, (page 265, right column, first paragraph) and a person of ordinary skill in the art would understand that target specificity of somatic hypermutation (SHM) may act similarly on genes that are expressed in B cells as taught by Storb, (page 13, right column, second paragraph), and

the regions of nucleic acid with a tendency of mutation may be influenced by methylation of specific cytosine residues as shown by Levy et al., (page 487; Figures 1-2; Tables 1-2) and a dataset of known mutations by Lippa et al. would allow one skilled in the art to distinguish gene regions of mutability with gene regions already known to contain mutations. Therefore, one of ordinary skill in the art would recognize the claimed process as a combination of routine applications that are well known the art that and produce no more than expected results.

Claims 1-3, 5-7, 9, 10, 12, 37, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. (Journal of Immunology, 1999, 163, 259-268) in view of Storb et al. (Phil. Trans. R. Soc. Lond. B., 2001, 356, 13-19), further in view of Levy et al. (J. Exp. Med., 1988, 168, 475-489) as applied to claims 1-3, 5-7, 9, 10, 37, 45 and 46 above, and further in view of Reiter et al. (Genome Research, 2001, 11, 1114-1125).

The instant claim 12 depends from claim 1 with the extra limitation that the dataset of two or more genes comprises a dataset of known diseases.

Shapiro et al. in view of Storb et al., in view of Levy et al. are applied to claims 1-3, 5-7, 9, 10, 37, 45 and 46 above.

Shapiro et al. in view of Storb et al. in view of Levy et al. do not show a dataset of genes with known diseases.

Regarding claim 12, Reiter et al. shows a dataset with genes with known mutations, (Table 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method predicting mutability in Ig V genes by Shapiro et al. by comparing other genes expressed in B lymphocytes such as BCL-6 genes of Storb et al., with the analysis of mutational regions of V genes with known methylation sites by Levy et al. and the use of a dataset of genes with known diseases by Reiter et al., because Shapiro et al. shows that the shared hierarchy of di- and trinucleotide target immutabilities among H and L chain V genes in mice and humans suggest that a common mutation mechanism acts on all Ig genes of both species, (page 265, right column, first paragraph) and a person of ordinary skill in the art would understand that target specificity of somatic hypermutation (SHM) may act similarly on genes that are expressed in B cells as taught by Storb, (page 13, right column, second paragraph), and the regions of nucleic acid with a tendency of mutation may be influenced by methylation of specific cytosine residues as shown by Levy et al., (page 487; Figures 1-2; Tables 1-2) and a dataset of known mutations by Reiter et al. would allow one skilled in the art to assess potential results of mutable genes and potential types of diseases. Therefore, one of ordinary skill in the art would recognize the claimed process as a combination of routine applications that are well known the art that and produce no more than expected results.

Claims 1-3, 5-7, 9, 10, 13-21, 37, 45-48 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. (Journal of Immunology, 1999, 163, 259-268) in view of Storb et al. (Phil. Trans. R. Soc. Lond. B., 2001, 356, 13-19), further

in view of Levy et al. (J. Exp. Med., 1988, 168, 475-489) as applied to claims 1-3, 5-7, 9, 10, 37, 45 and 46 above, and further in view of Smigielski et al. (Nucleic Acids Research, 2000, 28(1), 352-355).

The instant claims 13-21, 47, 48 and 52 depend from claim 1 with the extra limitation that the dataset of two or more genes comprises a type of database.

Shapiro et al. in view of Storb et al., in view of Levy et al. are applied to claims 1-3, 5-7, 9, 10, 37, 45 and 46 above.

Shapiro et al. in view of Storb et al. in view of Levy et al. do not show a dataset of genes comprising a database.

Regarding claims 13-21, 47, 48 and 52, Smigielski et al. shows a database of single nucleotide polymorphisms, (pages 352-353).

The only difference between the claimed invention and the teaching of Shapiro et al in view of Levy et al. and further in view of Smigielski et al. is the content of the database. The content of the database is nonfunctional descriptive material. The MPEP states in 2106 VI and 2106.01 in discussing computer related inventions in light of In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983):

> ***VI. DETERMINE WHETHER THE CLAIMED INVENTION COMPLIES***
>
> ***WITH 35 U.S.C. 102 AND 103***
>
> *Reviewing a claimed invention for compliance with 35 U.S.C. 102 and 103 begins with a comparison of the claimed subject matter to what is known in the prior art. See MPEP § 2131 - § 2146 for specific guidance on patentability determinations under 35 U.S.C. § 102 and 103. If no differences are found between the claimed invention and the prior art, then the claimed invention lacks novelty and is to be rejected by USPTO personnel under 35 U.S.C. 102. Once differences are identified between the claimed invention and the prior art, those differences must be assessed and resolved in light of*

the knowledge possessed by a person of ordinary skill in the art. Against this backdrop, one must determine whether the invention would have been obvious at the time the invention was made. If not, the claimed invention satisfies 35 U.S.C. 103.

2106.01

*When nonfunctional descriptive material is recorded on some computer-readable medium, in a computer or on an electromagnetic carrier signal, it is not statutory and should be rejected under 35 U.S.C. 101. In addition, USPTO personnel should inquire whether there should be a rejection under 35 U.S.C. 102 or 103. USPTO personnel should determine whether the claimed nonfunctional descriptive material be given patentable weight. USPTO personnel must consider all claim limitations when determining patentability of an invention over the prior art. In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 403-04 (Fed. Cir. 1983). USPTO personnel may not disregard claim limitations comprised of printed matter. See Gulack, 703 F.2d at 1384, 217 USPQ at 403; see also Diehr, 450 U.S. at 191, 209 USPQ at 10. However, USPTO personnel need not give patentable weight to printed matter absent a new and unobvious functional relationship between the printed matter and the substrate. See ** Lowry, 32 F.3d **>at< 1583-84, 32 USPQ2d **>at< 1035 **; In re Ngai, 367 F.3d 1336, 70 USPQ2d 1862 (Fed. Cir. 2004).*

Common situations involving nonfunctional descriptive material are:

- a computer-readable storage medium that differs from the prior art solely with respect to nonfunctional descriptive material, such as music or a literary work, encoded on the medium,

- a computer that differs from the prior art solely with respect to nonfunctional descriptive material that cannot alter how the machine functions (i.e., the descriptive material does not reconfigure the computer), or

- a process that differs from the prior art only with respect to nonfunctional descriptive material that cannot alter how the process steps are to be performed to achieve the utility of the invention.

Thus, if the prior art suggests storing a song on a disk, merely choosing a particular song to store on the disk would be presumed to be well within the level of ordinary skill in the art at the time the invention was made. The difference between the prior art and the claimed invention is simply a rearrangement of nonfunctional descriptive material.

The difference between Shapiro et al. in view of Storb et al. in view of Levy et al. and further in view of Smigielski et al. and the claimed invention constitutes non-functional descriptive material because the content of the database does not alter how the method of predicting mutability in genes, i.e., the data in the database does not limit the claimed method to predict mutations differently than the method of Shapiro et al. in view of Storb et al. in view of Levy et al. and further in view of Smigielski et al. Therefore no patentable weight is given to the databases in the claimed method.

Claims 1-3, 5-7, 9, 10, 13-21, 37, 45-48, 52 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. (Journal of Immunology, 1999, 163, 259-268) in view of Storb et al. (Phil. Trans. R. Soc. Lond. B., 2001, 356, 13-19), further in view of Levy et al. (J. Exp. Med., 1988, 168, 475-489) and further in view of Smigielski et al. (Nucleic Acids Research, 2000, 28(1), 352-355) as applied to claims 1-3, 5-7, 9, 10, 13-21, 37, 45-48 and 52 above.

The instant claim 56 is analogous to the method claims 13-21, 47, 48 and 52, except the method is performed in silico.

In *In re Venner*, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958), the court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplish the same result is not sufficient to distinguish over the prior art (see also *Manual of Patent Examining Procedure,* U.S. Trademark and Patent Office, section 2144.04, III).

In the instant case, the claimed invention merely makes the process of Shapiro et al., Storb et al., Levy et al. and Smigielski et al. performed in silico. Shapiro et al., Storb et al., Levy et al. and Smigielski et al. shows datasets comprising various databases which would include a human mutant database and a variation predictiveness matrix. It is thus not sufficient to distinguish over Shapiro et al., Storb et al., Levy et al. and Smigielski et al. Therefore, the claimed invention, i.e. the method of claims 13-21, 47, 48 and 52 wherein the step of generating the variation predictiveness matrix is performed in silico and the dataset of two or more genes comprises a human mutant database, would have been obvious to a person of ordinary skill in the art at the time the invention was made over the process disclosed by Shapiro et al., Storb et al., Levy et al. and Smigielski et al.

Furthermore, while Shapiro et al. Storb et al., Levy et al. and Smigielski et al. does not explicitly disclose performing in silico the process as in claims 13-21, 47, 48 and 52, they do disclose that all unmutated germline sequences were manipulated and analyzed with MACVECTOR version 5.0 software, (page 260, left column, fourth paragraph). Thus they at least disclose a computer readable medium comprising instructions for executing at least steps of analyzing sequences. Thus, the entire method of Shapiro et al., Storb et al., Levy et al. and Smigielski et al. could be interpreted as semi-automatic. One of ordinary skill in the art would have been motivated to make it perform the method of claims 13-21, 47, 48 and 52 in silico to take the obvious advantage of a fully automatic process, i.e. saving time and cost.

There would have been a reasonable expectation of success because the court held regarding software that "writing code for such software is within the skill of the art, not requiring undue experimentation, once its functions have been disclosed." Fonar Corp., 107 F.3d at 1549, 41 USPQ2d at 1805.

Claims 53, 57, 203 and 204 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. (Journal of Immunology, 1999, 163, 259-268) in view of Storb et al. (Phil. Trans. R. Soc. Lond. B., 2001, 356, 13-19), as applied to claims 1, 45 and 46 above.

The instant claims 53, 57, 203 and 204 are analogous to the method claim 1, except the method is effected by a computer program (claim 53), performed in silico (claim 57), drawn to a computer readable medium encoded with a computer program executable by a processor for predicting variations in a wild-type gene sequence (claim 203) or codons in a wild-type gene sequence (claim 204).

In *In re Venner*, 262 F.2d 91, 95, 120 USPQ 193, 194 (CCPA 1958), the court held that broadly providing an automatic or mechanical means to replace a manual activity which accomplish the same result is not sufficient to distinguish over the prior art (see also *Manual of Patent Examining Procedure,* U.S. Trademark and Patent Office, section 2144.04, III).

In the instant case, the claimed invention merely makes the process of Shapiro et al. in view of Storb et al. as a method effected by a computer program, performed in silico or as a computer readable medium with code and indeed accomplishes the same

result. Shapiro et al. in view of Storb et al. shows predicting mutability in wild-type gene sequences (unmutated sequence) and codons, (page 260, left column, fourth paragraph; Figure 7). It is thus not sufficient to distinguish over Shapiro et al. in view of Storb et al. Therefore, the claimed invention, i.e. performing the method in silico or the computer readable medium comprising instructions to execute a process would have been obvious to a person of ordinary skill in the art at the time the invention was made over the process disclosed by Shapiro et al. in view of Storb et al.

Furthermore, while Shapiro et al. in view of Storb et al. does not explicitly disclose performing in silico or a computer medium comprising instructions for executing all the steps of the process as in claim 1, they do disclose that all unmutated germline sequences were manipulated and analyzed with MACVECTOR version 5.0 software, (page 260, left column, fourth paragraph). Thus they at least disclose a computer readable medium comprising instructions for executing at least steps of analyzing sequences. Thus, the entire method of Shapiro et al. in view of Storb et al. could be interpreted as semi-automatic. One of ordinary skill in the art would have been motivated to make it completely automatic by performing the method in silico or comprising instructions in the computer readable medium for executing all steps of the method to take the obvious advantage of a fully automatic process, i.e. saving time and cost.

There would have been a reasonable expectation of success because the court held regarding software that “writing code for such software is within the skill of the art,

not requiring undue experimentation, once its functions have been disclosed." Fonar Corp., 107 F.3d at 1549, 41 USPQ2d at 1805.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LARRY D. RIGGS II whose telephone number is (571)270-3062. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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